REMARKS/ARGUMENTS

Claims 119-123 are pending in this application. Applicants thank the Examiner for withdrawing the continuity objection. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 119-123 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 3 of the instant Office Action). Claims 119-123 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention." (Page 19 of the instant Office Action). Applicants respectfully disagree with and traverse these rejections.

The Examiner asserts that since the protein of the invention is not supported by a specific and substantial asserted utility or well established utility, the encoding polynucleotides, chimeric proteins and antibodies also lack utility.

Utility Guidelines

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention

must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, Emphasis added.). Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, §2107 II(B)(1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. §2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.**

Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. The issue will then be decided on the totality of evidence.

Arguments

The Examiner alleges that "the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue...."(Page 4 of the instant Office Action).

Applicants first respectfully point out that the observed increase in PRO1097 gene amplification in lung and colon tumor is not "small" but **significant**, as has been discussed in detail in the previous responses and the Appeal Brief filed August 22, 2005. Applicants have

repeatedly argued that gene amplification, an essential mechanism for oncogene activation, is well-described in Example 170, page 539 of the present application. Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9B. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on." (Emphasis added). Applicants show that PRO1097 showed approximately 1.21-1.23 ΔCt units which corresponds to $2^{1.21}$ -$2^{1.23}$- fold amplification or **2.313 to 2.346-fold** amplification in lung tumors and 1.08-1.34 ΔCt units which corresponds to $2^{1.08}$ -$2^{1.34}$- fold amplification or **2.114 to 2.532-fold** amplification in colon tumors, which is significant and thus the PRO1097 gene has utility as a diagnostic marker of human lung and colon cancer.

The Examiner maintains that the Ornoft *et al.*, reference is not persuasive because "it is not clear whether or not PRO1097 is in a gene cluster region of a chromosome that is highly amplified," such as those characterized by Ornoft. (Page 10 of the instant Office Action).

The Ornoft reference was submitted by the Applicants with their Response of September 10, 2004, was discussed in detail therein, and was further discussed in the Appeal Brief filed on August 22, 2005. Ornoft was submitted to show that there was a gene dosage effect and teaches that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). Based on this reference and on several other references submitted in the IDS filed with the last response, Applicants have submitted that it is generally well-understood in the art that DNA copy number influences gene expression. For example, Ornoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers which were linked to a gain/loss of chromosomal material using an array-based method.

Applicants submit that the DNA encoding PRO1097 would have utility even if it were shown not to be in a gene cluster, because the instant specification has already determined that the PRO1097 DNA is amplified significantly compared to its control. Applicants have provided an expert Declaration (the Goddard Declaration) to support the significance of the values obtained in the gene amplification assay for PRO1097 DNA. Therefore, a utility rejection based

on the premise that PRO1097 DNA may not be within an amplified cluster is not appropriate according to the utility standards.

The Examiner also repeats her rejection based on Pennica *et al.*, asserting that matched tissue samples are the standard in the literature, and further repeats the rejection based on Sen *et al.*, asserting that the data were not corrected for aneuploidy. (Page 4 of the instant Office Action).

Applicants respectfully submit that the negative control *i.e.,* the "pooled normal blood controls" taught in the specification was known in the art at the time of filing, and accepted as a true negative control as demonstrated by use in peer reviewed publications. For example, in Pitti *et al.* (Exhibit F of Dr. Audrey Goddard's Declaration submitted with the Appeal Brief filed on August 22, 2005), the authors used the same quantitative TaqMan PCR assay described in the specification to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. As described, Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1; Emphasis added). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.* (Exhibit G of Dr. Audrey Goddard's Declaration submitted with the Appeal brief filed on August 22, 2005), the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2), thus confirming the validity of the negative control. Accordingly, the art demonstrates that pooled normal blood samples are considered to be a valid negative control for gene amplification experiments of the type described in the specification.

The Examiner further asserts that "[U]tilization of incorrect tissue for comparison (with the absence of, or diminished expression of a gene in a particular tissue) would artificially increase or decrease the magnitude of differences observed in the instant assay. Likewise, using

tumor and control samples from *different* subjects introduces variability into gene amplification assay, making it less compatible and accurate." (Page 14 of the instant Office Action).

Applicants respectfully submit that all normal tissues have the same gene copy numbers. Accordingly, there is no requirement to match tissues or sample subjects in an assay designed to measure gene amplification.

Sen *et al.*

Sen *et al.* indicates that aneuploidy can be a feature of damaged, pre-cancerous tissue and cancerous tissue. Sen *et al.* in fact support the Applicants' position that PRO1097 is still useful in diagnosing at least pre-cancerous lesions or cancer itself. Many articles published around June 23, 1999 (the effective filing date of this application) studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of colon cancer. Based on the well-known art, Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

Taken together, even if the observed PRO1097 gene amplification were due to chromosomal aneuploidy (which Applicants do not concede), such an observation would actually support utility for the PRO1097 gene. Whether PRO1097's gene amplification is due to aneuploidy or not, it helps identify pre-cancerous or cancerous lung or colon lesions and thus, helps in identifying individuals at significantly increased cancer risk. One skilled in the art would clearly have known the value of early detection for cancer, and would have welcomed information in advance about cancer risk, which would help in the prognosis and therapy for lung or colon cancer. Accordingly, the instant antibodies find utility as a diagnostic for lung or colon cancer, or at least for identifying individuals at risk for developing lung or colon cancer.

The Examiner also cites references by Hu *et al.*, Pennica *et al.*, Haynes *et al.*, and Chen *et al.*, in support of the assertion that " increased mRNA levels are frequently not predictive of increased polypeptide levels." (Pages 16-17 of the instant Office Action).

Applicants respectfully remind the Examiner that the evidentiary standard to be used throughout ex parte examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must

establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter, such that the overexpression of every possible gene inevitably results in protein overexpression. The law requires only that one skilled in the art should accept that such a correlation is more likely than not to exist. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants are asserting that a measurable change in gene amplification level (for example, in tumor as compared to normal tissue) generally leads to a corresponding change in the level of mRNA and protein expression. Applicants further note that what is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. A showing that gene or mRNA levels can be used to accurately predict the precise levels of protein expression is not required. Applicants need only show that there is a correlation between DNA, mRNA, and protein levels, such that gene amplification and mRNA overexpression generally predict protein overexpression.

Chen *et al.*

The Examiner cites Chen *et al.* as comparing mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. "twenty-eight of the 165 protein blots(17%) or 21 of 98 genes (21.4%) had a statistically significant correlation between protein and mRNA expression (see Abstract and Table I). In addition, their results showed that no significant correlation between mRNA and protein expression was found (r= -0.025)." (Page 8 of the instant Office Action).

The manner in which the Chen data was averaged and analyzed is a vastly different manner from that of the instant specification. For example, Chen *et al.* studied expression levels across a set of samples which included a large number of tumor samples (76) and a much smaller group of normal samples (9). The authors determined the global relationship between mRNA and corresponding protein expression using the average expression values for all 85 lung tissue samples. The authors chose an arbitrary threshold of 0.115 for the correlation to be considered

significant. This resulted in negative normalized protein values in some cases and the authors concluded that it is not possible *to predict* overall protein expression based on **average mRNA abundance**. Applicants remind the Examiner that the utility standard does not require accurate prediction of protein values; only that in a majority of the proteins studied, it is more likely than not that protein levels increased when mRNA levels increased. A review of the correlation coefficient data presented in the Chen *et al.* paper indicates that, in fact, Chen teaches that 'it is more likely than not' that increased mRNA expression correlates well with increased protein expression. For instance, a review of Table 1, which lists 66 genes [the paper incorrectly states there are 69 genes listed] for which only one protein isoform is expressed, shows that 40 genes out of 66 had a positive correlation between mRNA expression and protein expression. This clearly meets the test of "more likely than not." Similarly, in Table II , 30 genes with multiple isoforms [again the paper incorrectly states there are 29] were presented. In this case, for 22 genes out of 30, at least one isoform showed a positive correlation between mRNA expression and protein expression. Furthermore, 12 genes out of 29 showed a strong positive correlation [as determined by the authors] for at least one isoform. **No genes showed a significant negative correlation**. It is not surprising that not all isoforms are positively correlated with mRNA expression. Thus, Table II also provides that it is more likely than not that protein levels will correlate with mRNA expression levels.

With respect to Futcher *et al*, the Examiner asserts that "Futcher *et al.* indicates that 'Gygi *et al.* feel that mRNA abundance is a poor predictor of protein abundance.'" (Page 11 of the instant Office Action).

Applicants respectfully point out that, on the contrary, Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient to **accurately** predict the protein level from the level of the corresponding mRNA transcript (see page 1270, Abstract). Contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels. (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies/cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell. (Emphasis added). Therefore, high levels of mRNA **generally**

correlate with high levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein.

Gygi *et al.* may teach that protein levels cannot be "predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Applicants respectfully submit that the PTO's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Applicants need only show that there is a correlation between mRNA and protein levels, such that mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

Moreover, Futcher *et al.* point out that the "different conclusions" of Gygi *et al.* are also partly due to different methods of statistical analysis, and to real differences in data. Futcher *et al.* note that Gygi *et al.* used the Pearson product-moment correlation coefficient (r_p) and point out that "a calculation of r_p is inappropriate" because the mRNA and protein abundances are not normally distributed (page 7367, col. 1). In contrast, Futcher *et al.* used two different statistical approaches to determining the correlation between mRNA and protein abundances. First, they used the Spearman rank correlation coefficient (r_s), an nonparametric statistic that does not require the data to be normally distributed. Using the r_s, the authors found that mRNA abundance was well correlated with protein abundance ($r_s = 0.74$). Applying this statistical approach to the data of Gygi *et al.* **also** resulted in a good correlation ($r_s = 0.59$), although the correlation was not quite as strong as for the Futcher *et al.* data. In a second approach, Futcher *et al.* transformed the mRNA and protein data to forms where they were normally distributed, in order to allow calculation of an r_p. Two types of transformation (Box-Cox and logarithmic) were used, and **both** resulted in good correlations between mRNA and protein abundance for Futcher *et al.*'s data.

Futcher *et al.* also note that the two studies used different methods of measuring protein abundance. Gygi *et al.* cut spots out of each gel and measured the radiation in each spot by

scintillation counting, whereas Futcher *et al.* used phosphorimaging of intact gels coupled to image analysis. Futcher *et al.* point out that Gygi *et al.* may have systematically overestimated the amount of the lowest-abundance proteins, because of the difficulty in accurately cutting out very small spots from the gel, and because of difficulties in background subtraction for small, weak spots.

In addition, Futcher *et al.* note that they used both SAGE data and RNA hybridization data to determine mRNA abundances, which is most helpful to accurately measure the least abundant mRNAs. As a result, while the Futcher data set "maintains a good correlation between mRNA and protein abundance even at low protein abundance" (page 7367, col. 2), the Gygi data shows a strong correlation for the most abundant proteins, but a poor correlation for the least abundant proteins in their data set. Futcher *et al.* conclude that "**the poor correlation of protein to mRNA for the nonabundant proteins of Gygi *et al.* may reflect difficulty in accurately measuring these nonabundant proteins and mRNAs, rather than indicating a truly poor correlation *in vivo.***" (Page 7367, col. 2; Emphasis added). Thus, while these lowest abundant proteins do show a poor correlation, this is almost certainly due to the less accurate methods used to measure the abundance of these proteins, and **not** to any actual lack of correlation.

With respect to the Second Declaration of Dr. Polakis, submitted with Applicants' Preliminary Amendment filed July 5, 2006, the Examiner alleges that " Dr. Polakis refers to facts; however, the data are not included in the Declaration so that the Examiner could independently evaluate them." (Page 17 of the instant Office Action).

Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art. Further, the Examiner has not presented any convincing evidence to indicate that one of ordinary skill in the art would doubt the validity of anti-PRO1097 antibodies have utility in the diagnosis of cancer.

The Examiner notes that Dr. Polakis is employed by the assignee. (Page 17 of the instant Office Action).

Applicants note that the sworn Declaration of Dr. Polakis is sufficient to support Applicants' position that the gene amplification influences gene expression at the mRNA and protein levels.

Taken together, despite some teachings in the art of certain genes that do not fit within this paradigm which are exceptions rather than the rule, in the vast majority of amplified genes, the combined teachings in the art as exemplified by Orntoft *et al.* and other references discussed and submitted in this case, as well as the Polakis Declaration, overwhelmingly teach that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect, in this instance, based on the amplification data for the PRO1097 gene, that the PRO1097 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO1097 proteins have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use these molecules.

The Examiner alleges " there is no guidance in the specification as to the values above the "cutoff ratio" or how high the levels of overexpression are." (Page 14 of the instant Office Action).

Applicants draw the Examiner's attention to the fact that the present data relates to "gene amplification data," not microarray data. "Cutoff ratio" is neither referred to nor described in the instant specification. Since references to "cutoff ratio" values are not relevant, this rejection is moot.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the anti-PRO1097 antibodies, for example, in detecting over-expression or absence of expression of PRO1097. In fact, the art also indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will also be expressed at an elevated level. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed polypeptides. Hence, these data clearly support a role for PRO1097 and the claimed antibodies that bind it, as a lung or colon tumor marker.

Accordingly, the present 35 U.S.C. §101 and §112, first paragraph, utility rejections should be withdrawn.

Claim Rejections - 35 U.S.C. §112, First Paragraph - Enablement

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, as allegedly "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Pages 19 of the instant Office Action).

Applicants respectfully traverse this rejection. Based on the discussions above under utility for the anti-PRO1097 antibodies in the diagnosis of lung or colon cancer, Applicants submit that the skilled artisan would not require undue experimentation to make and use the claimed invention.

Accordingly, Applicants request that this rejection be withdrawn.

CONCLUSION

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730P1C30**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 10, 2007

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